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(54) **alpha-Aryl-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)benzeneacetonitriles.**

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**FR-A-2 231 378**
**US-A-3 912 723**

**JOURNAL OF MEDICINAL CHEMISTRY, vol. 26, 1983, pages 96-100, American Chemical Society, Washington, US; R.D. CARROLL et al.: "Anticoccidial derivatives of 6-azauracil. 5. Potentiation by benzophenone side chains"**

**The file contains technical information submitted after the application was filed and not included in this specification**

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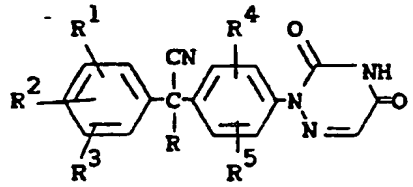
## Description

2-Phenyl-as-triazine-3,5-(2*H*,4*H*) diones and their use for controlling coccidiosis have been described in U.S. Pat nt No. 3,912,723. The phenyl moiety in the said triazines may, inter alia, be substituted with a benzoyl-, a α-hydroxy-phenylmethyl- and a phenylsulfonyl radical.

J. Med. Chem. 1983, *26*, 96—100 similarly describes a series of 2-phenyl-triazine-3,5-(2*H*,4*H*) diones possessing coccidiostatic activity.

The 2-phenyl-as-triazine-3,5-(2*H*,4*H*)diones, described in the present application, differ from the hereinabove-mentioned triazinones, by the substitution of the phenyl moiety with a α-cyano-phenylmethyl radical, resulting in triazine-3,5-(2*H*,4*H*)diones which are very effective in destructing or preventing the growth of *Protozoa* in subjects suffering from such *Protozoa*.

The present invention is related with α-aryl-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)benzeneacetonitriles having the formula



(I)

the pharmaceutically acceptable acid addition salts and the possible stereochemically isomeric forms thereof, wherein:

$R^1$, $R^2$ and $R^3$ are each independently hydrogen, halo, trifluoromethyl, $C_{1-6}$ alkyl, $C_{1-6}$ alkyloxy, $C_{1-6}$ alkylthio or $C_{1-6}$ alkylsulfonyl;

$R^4$ and $R^5$ are each independently hydrogen, halo, trifluoromethyl or $C_{1-6}$ alkyl; and

R is hydrogen, $C_{1-6}$ alkyl, cyclo $C_{3-6}$ alkyl or phenyl optionally substituted with up to three substituents each independently selected from the group consisting of halo, trifluoromethyl, $C_{1-6}$ alkyl, $C_{1-6}$ alkyloxy, $C_{1-6}$ alkylthio and $C_{1-6}$ alkylsulfonyloxy.

In the foregoing definitions the term "halo" is generic to fluoro, chloro, bromo and iodo; "$C_{1-6}$ alkyl" is meant to include straight and branched saturated hydrocarbon radicals, having from 1 to 6 carbon atoms, such as, for example, methyl, ethyl, 1-methylethyl, 1,1-dimethylethyl, propyl, butyl, pentyl, hexyl, and the like; "cyclo $C_{3-6}$ alkyl" embraces cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

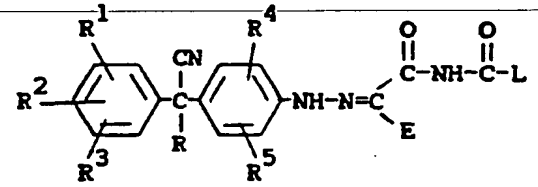
Preferred compounds within the invention are those wherein $R^1$ and $R^2$ are, each independently, hydrogen, halo, $CF_3$, or $C_{1-}$ alkyl; $R^3$ is hydrogen; R is hydrogen, $C_{1-6}$ alkyl, phenyl or halophenyl; $R^4$ and $R^5$ are, each independently, hydrogen, halo, $CF_3$ or $C_{1-6}$ alkyl.

More preferred compounds within the invention are those wherein $R^1$ is halo; $R^2$ and $R^3$ are both hydrogen; R is hydrogen, $C_{1-6}$ alkyl or halophenyl; and $R^4$ and $R^5$ are as described hereinabove for the preferred compounds.

Particularly preferred compounds within the invention are those wherein $R^1$ is 4-halo, $R^2$ and $R^3$ are both hydrogen, R is hydrogen or methyl and $R^4$ and $R^5$ are each independently hydrogen, halo, methyl or trifluoromethyl, said $R^4$ and $R^5$ are beiong substituted on the 2 and/or 6 position of the phenyl moiety bearing said $R^4$ and $R^5$.

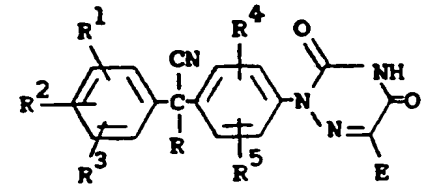
The most preferred compounds of the present invention are selected from the group consisting of 2-chloro-α-(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)benzeneacetonitrileand2,6-dichloro-α-(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)benzeneacetonitrile, the pharmaceutically acceptable acid-addition salts and possible stereochemically isomeric forms thereof.

The compounds of formula (I) may generally be prepared by cyclizing an intermediate of formula



(II)

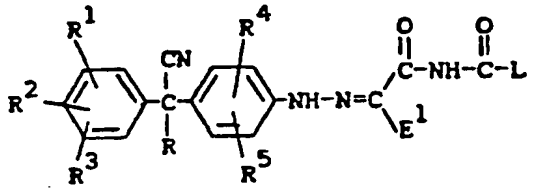
and eliminating the group E of the thus obtained dione



(III)

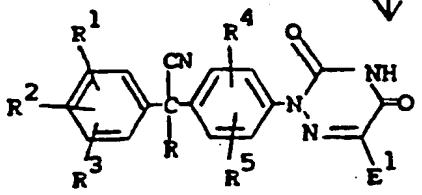
In the intermediates (II) L has the meaning of an appropriate leaving group such as $C_{1-6}$ alkyloxy, halo and the like. The group E, as described in the intermediate (II) and the triazinedione (III), represents an appropriate electron attracting gr up which may conveniently be eliminated from the dione (III) such as, for example, a carboxyl, a sulfonyloxy, a sulfinyloxy group or a precursor and/or derivative thereof, e.g. an ester, an amide, a cyanide, a $C_{1-6}$ alkylsulfonyloxy, phenylsulfonyloxy, $C_{1-6}$ alkylphenylsulfonyloxy and halophenylsulfonyloxy and the like groups.

A particularly suitable process for preparing compounds of formula (I) consists of cyclizing an intermediate of formula (II-a) and eliminating the $E^1$ functionality in the thus obtained intermediate of formula (III-a). In (II-a) and (III-a) $E^1$ represents a cyano, $C_{1-6}$ alkyloxycarbonyl or amide group.



(II-a)

cyclization reaction

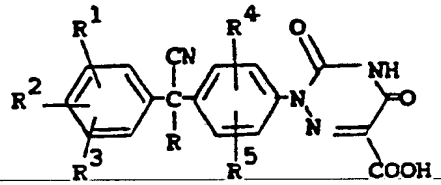


(III-a) ⟶ (I)

The cyclization reaction may be effected following art-known cyclization procedures as described, for example, in Monatshefte der Chemie, *94*, 258—262 (1963), e.g. by heating the starting compound of formula (II-a) above its melting point, or by refluxing a mixture of (II-a) with a suitable solvent such as, for example, an aromatic hydrocarbon, e.g. benzene, methylbenzene, or dimethylbenzene, an acid, e.g. acetic acid, optionally in the presence of base, e.g. potassium acetate, sodium acetate and the like.

The elimination of the $E^1$ functionality may be effected following art-known procedures as described, for example, in Monatshefte der Chemie, *96*, 134—137 (1965), e.g. by converging (III-a) into a carboxylic acid (IV) in a suitable acidic reaction medium such as acetic acid, aqueous hydrochloric acid solutions or mixtures thereof. Elevated temperatures may enhance the rate of the reaction.

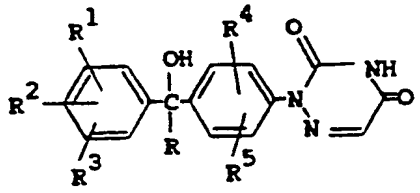
The thus obtained carboxylic acids of formula



(IV)

may be converted into a compound of formula (I) by art-known decarboxylation reaction procedures, e.g. by heating the carboxylic acid (IV) or by heating a solution of (IV) in 2-mercaptoacetic acid as described, for example, in US Patent No. 3,896,124.

The compounds of formula (I) may also generally be prepared by converting the hydroxyl function of a triazinedione of formula

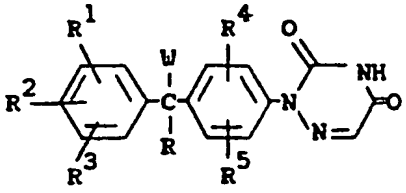


(V)

into a nitrile function.

The conversion of (V) into (I) may b effected by art-known procedures. F r exampl , by first

converting the hydroxy function into a suitable leaving group and subsequently converting the said leaving group in the thus obtained



(VI)

into a nitrile function.

In (VI) W has the meaning of an appropriate reactive leaving group such as, for example, halo, e.g., chloro, bromo or iodo, or a sulfonyloxy group, e.g. methylsulfonyloxy or 4-methylphenylsulfonyloxy.

For example, where W represents chloro, the intermediates (VI) may be prepared by reacting (V) with thionyl chloride in a suitable reaction-inert solvent.

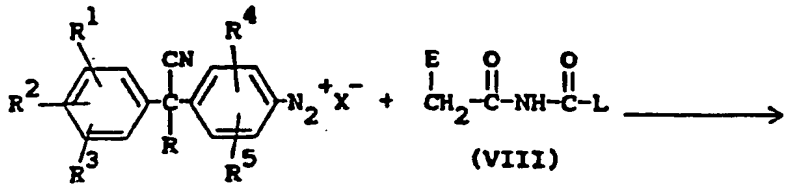
The conversion of (VI) into (I) may be effected, for example, by reacting (VI) with a cyanide, such as, for example, a alkalimetal cyanide, e.g. potassium cyanide, sodium cyanide; copper cyanide; silver cyanide and the like, if desired, in the presence of an appropriate solvent.

The compounds of formula (I) have basic properties and, consequently, they may be converted to their therapeutically active non-toxic acid addition salt forms by treatment with appropriate acids, such as, for example, inorganic acids, such as hydrohalic acid, e.g. hydrochloric, hydrobromic and the like, and sulfuric acid, nitric acid, phosphoric acid and the like; or organic acids, such as, for example, acetic, propanoic, hydroxyacetic, 2-hydroxy-propanoic, 2-oxopropanoic, ethanedioic, propanedioic, butanedioic, (Z)-2-butenedioic, (E)-2-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids. Conversely the salt form can be converted by treatment with alkali into the free base form.

It is obvious from formula (I) that the compounds of the present invention have an asymmetric carbon atom. Consequently, these compounds may exist under two different enantiomeric forms. Pure enantiomeric forms of the compounds of formula (I) may be obtained by the application of art-known procedures.

A number of intermediates and starting materials in the foregoing preparations are known compounds which may be prepared according to art-known methodologies of preparing said or similar compounds. A number of such preparation methods will be described hereinafter in more detail.

The intermediates of formula (II) may generally be prepared by reacting a diazonium salt of formula (VII) with a reagent of formula (VIII).

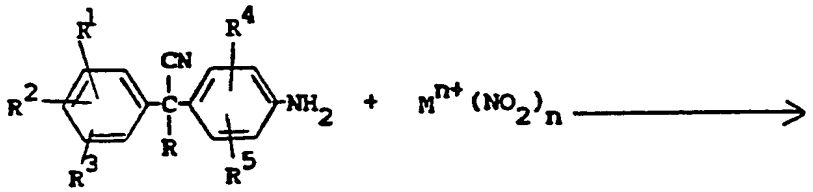


(VII) (VIII) (II)

$X^-$, as described in (VII) has the meaning of an appropriate anion and E and L, as described in (VII), have the previously defined meanings.

The reaction of (VII) with (VIII) may conveniently be conducted in a suitable reaction medium as described, for example, in Monatshefte der Chemie, *94*, 694—697 (1963). Suitable reaction mediums are, for example, aqueous sodium acetate solutions, pyridine and the like.

The starting diazonium salts (VII) may be derived from a corresponding amine of formula (IX) following art-known procedures by reacting the latter with an alkalimetal or earth alkaline metal nitrite, e.g. sodium nitrite, in a suitable reaction medium.



(IX) (VII)

In the hereinabove-described reaction scheme $M^{n+}$ is a alkalimetal or earth alkaline metal kati n and n is the int g r 1 r 2.

The amines of formula (IX) may be prepared following procedures analogous to those described in U.S. Patent No. 4,005,218.

The triazinedi nes of formula (VI) may be prepared following the procedures described in US Patent No. 3,912,723.

The intermediates of formula (II) and (III), and more particularly, the intermediates of formula (II-a), (III-a) and (IV), said intermediates being useful in the preparation of the compounds of formula (I), are deemed to be novel and this constitutes an additional feature of the present invention.

The compounds of formula (I), the pharmaceutically acceptable acid addition salts and the possible stereochemically isomeric forms thereof are useful agents in combatting *Protozoa*. For example, said compounds are found to be active against a wide variety of said *Protozoa* such as, for example, *Sarcodina, Mastigophora, Ciliophora* and *Sporozoa.*

The compounds of formula (I), the pharmaceutically acceptable acid addition salts and the possible stereochemically isomeric forms thereof are especially useful agents in combatting *Rhizopoda* such as, for example, *Entamoeba;* and *Mastigophora* such as, for example, *Trichomonas,* e.g. *Trichomonas vaginalis, Histomonas,* e.g. *Histomonas maleagridis,* and *Trypanosoma* spp.

In view of their potent activity in combatting *Protozoa* the compounds of this invention constitute useful tools for the destruction or prevention of the growth of *Protozoa* and more particularly they can effectively be used in the treatment of subjects suffering from such *Protozoa.*

In view of their potent activity in combatting *Protozoa* this invention provides valuable compositions comprising the compounds of formula (I), the acid addition salts or possible stereochemically isomeric forms thereof, as the active ingredient in a solvent or a solid, semi-solid or liquid diluent or carrier, and, in addition, it provides an effective method of combatting *Protozoa* by use of an effective anti-protozoal amount of such compounds of formula (I), or acid addition salts thereof. Anti-protozoal compositions comprising an effective amount of an active compound of formula (I), either alone or in combination with other active therapeutic ingredients, in admixture with suitable carriers may be readily prepared according to conventional pharmaceutical techniques for the usual routes of administration.

Preferred compositions are in dosage unit form, comprising per dosage unit an effective quantity of the active ingredient in admixture with suitable carriers. Although the amount of the active ingredient per unit dosage may vary within rather wide limits, dosage units comprising from about 10 to about 2000 mg of the active ingredient are preferred.

In view of the anti-protozoal properties of the compounds of formula (I) it is evident that the present invention provides a method of inhibiting and/or eliminating the development of *Protozoa* in warm-blooed animals suffering from diseases caused by one or more of those *Protozoa* by the administration of an antiprotozoal effective amount of a compound of formula (I), a pharmaceutically acceptable acid addition salt or a possible stereochemically isomeric form thereof.

More particularly, in view of their extremely potent activity in combatting *Coccidia* the compounds of this invention are very useful in the destruction or prevention of the growth of Coccidia in warm-blooded animals. Consequently, the compounds of formula (I), the acid addition salts and possible stereochemically isomeric forms thereof are particularly useful anti-coccidial agents as well as coccidiostats.

Due to their useful anti-coccidial and coccidiostatic activity the subject compounds may be administered in combination with any solid, semi-solid or liquid diluent or carrier as described hereinabove. Additionally, due to their useful coccidiostatic activity the subject compounds may be mixed with any kind of feed supplied to warm-blooded animals although it may also be administered while dissolved or suspended in the drinking water.

The following examples are intended to illustrate and not to limit the scope of the present invention.

Unless otherwise stated all parts therein are by weight.

## EXAMPLES

A) Preparation of Intermediates.

### Example 1

A mixture of 68 parts of 4-fluorobenzeneacetonitrile, 180 parts of ethyl carbonate, 100 parts of a sodium methoxide solution 30% and 200 parts of dimethylbenzene was distilled till an internal temperature of 110°C was reached. The distillate was cooled and 80 parts of 2-propanol were added, followed by the dropwise addition of 63 parts of methyl sulfate at room temperature (exothermic reaction: temperature rose to 80°C). The remaining 120 parts of 2-propanol were added while stirring vigorously. Upon completion, stirring was continued for 20 hours. Then there were added 56 parts of potassium hydroxide (exothermic reaction: temperature rose to 75°C). The whole was stirred and refluxed for 30 minutes. The reaction mixture was cooled and poured into 750 parts of water. The aqueous phase was separated and extracted with methylbenzene. The extract was dried, filtered and evaporated. The oily residue was distilled, yielding 54 parts of 4-fluoro-α-methylbenzeneacetonitrile; bp. 110—115°C at 11 mm. pressure (intermediate 1).

Example 2

To a stirred solution of 20 parts of 1,2-dichloro-4-nitrobenzene in 160 parts of pyridine was added a paste of 28 parts of solid potassium hydroxide and 40 parts of pyridine. After cooling to 5°C, there was added dropwise 15.6 parts of 4-fluoro-α-methylbenzeneacetonitrile. Upon completion, the whole was further stirred f r 10 h urs at −5°C. The cooling bath was removed and the reaction mixture was diluted with 80 parts of benzene. The whole was filtered and the filtrate was evaporated. The residue was poured into water and the product was extracted with methylbenzene. The latter was dried, filtered and evaporated. The solid residue was crystallized from a mixture of 1,1'-oxybisethane and benzene, yielding 15 parts of α-(2-chloro-4-nitrophenyl)-4-fluoro-α-methylbenzeneacetonitrile; mp. 133.1°C (intermediate 2).

Example 3

To a stirred mixture of 45.3 parts of 1,2,3-trichloro-5-nitrobenzene, 300 parts of a sodium hydroxide solution 50%, 5 parts of *N,N,N*-triethylbenzenemethanaminium chloride and 360 parts of tetrahydrofuran was added dropwise, during a 5 minute period, a solution of 33.3 parts of 4-chlorobenzeneacetonitrile in 90 parts of tetrahydrofuran. Upon completion, stirring was continued for 4 hours at 50°C. The reaction mixture was poured into 1500 parts of crushed ice and acidified with concentrate hydrochloric acid. The product was extracted with triochloromethane. The extract was dried, filtered off and dried, yielding 63.8 parts (93.3%) of 2,6-dichloro-α-(4-chlorophenyl)-4-nitrobenzeneacetonitrile (intermediate 3).

Following the same procedure and using equivalent amounts of the appropriate starting materials, there were also prepared:

4-chloro-α-(2-chloro-4-nitrophenyl)-α-methylbenzeneacetonitrile; mp. 139.3°C (intermediate 4);

2-chloro-α-(4-chlorophenyl)-4-nitrobenzeneacetonitrile (intermediate 5); α-(4-chlorophenyl)-α-methyl-4-nitro-2-(trifluoromethyl)benzeneacetonitrile (intermediate 6);

2-chloro-α,α-bis(4-chlorophenyl)-4-nitrobenzeneacetonitrile (intermediate 7);

2-chloro-α-(4-chlorophenyl)-5-methyl-4-nitrobenzeneacetonitrile (intermediate 8);

2-fluoro-α-(4-fluorophenyl)-4-nitrobenzeneacetonitrile (intermediate 9):

2,6-dichloro-α-(4-fluorophenyl)-4-nitrobenzeneacetonitrile (intermediate 10);

2-chloro-α-(4-fluorophenyl)-6-methyl-4-nitrobenzeneacetonitrile (intermediate 11))

α-(4-fluorophenyl)-2,6-dimethyl-4-nitrobenzeneacetonitrile (intermediate 12); and

2-chloro-α-(4-chlorophenyl)-5-methyl-4-nitrobenzeneacetonitrile (intermediate 13).

Following the same procedures and using the appropriate starting materials there are also prepared:

2-chloro-α-(4-chlorophenyl)-6-methyl-4-nitrobenzeneacetonitrile (intermediate 14);

2-chloro-α-(4-fluorophenyl)-4-nitrobenzeneacetonitrile (intermediate 15); and

2-chloro-α-(4-methylphenyl)-4-nitrobenzeneacetonitrile (intermediate 16).

Example 4

To a stirred mixture of 14.2 parts of iodomethane, 153 parts of a sodium hydroxide solution 50%, 1 part of *N,N,N*-triethylbenzenemethanaminium chloride and 67.5 parts of tetrahydrofuran was added dropwise, during a period of 15 minutes, a solution of 37.5 parts of 2-chloro-α-[4-chloro-3-(trifluoromethyl)phenyl]-4-nitrobenzeneacetonitrile in 67.5 parts of tetrahydrofuran. The reaction mixture was stirred and heated for 4 hours at 50—60°C. Another portion of 2.3 parts of iodomethane was added and the whole was stirred for 1 hour at 50°C. The mixture was poured into 1000 parts of crushed ice. The whole was acidified with concentrate hydrochloric acid. The product was extracted with trichloro-methane. The extract was dried, filtered and evaporated. The residue was stirred in 160 parts of ethanol. The product was filtered off, washed with 2,2'-oxybispropane and dried, yielding 34.2 parts (87.8%) of 4-chloro-α-(2-chloro-4-nitrophenyl)-α-methyl-3-(trifluoromethyl)benzeneacetonitrile; mp. 162.5°C (intermediate 17).

In a similar manner there were also prepared:

2-chloro-α-(4-chlorophenyl)-4-nitro-α-propylbenzeneacetonitrile (intermediate (18);

α-butyl-2-chloro-α-(4-chlorophenyl)-4-nitrobenzeneacetonitrile (intermediate (19);

2,6-dichloro-α-(4-chlorophenyul)-α-methyl-4-nitrobenzeneacetonitrile (intermediate (20);

2-chloro-α-(4-chlorophenyl)-α,6-dimethyl-4-nitrobenzeneacetonitrile (intermediate (21);

2-chloro-α-(4-chlorophenyl)-α,5-dimethyl-4-nitrobenzeneacetonitrile (intermediate (22); and

2-fluoro-α-(4-fluorophenyl)-α-methyl-4-nitrobenzeneacetonitrile (intermediate (23).

Example 5

A mixture of 20 parts of 4-chloro-α-(2-chloro-4-nitrophenyl)-α-methylbenzeneacetonitrile, 7 parts of iron powder, 250 parts of ammonium chloride solution 0.78N and 200 parts of methylbenzene was stirred and refluxed for 3 hours. The reaction mixture was filtered hot. The aqueous phase was separated and washed with methylbenzene. The combined organic layers were washed successively with water, sodium hydrogen carbonate solution and again with water, dried and evaporated. The residue was washed with 1,1'-oxybisethane and dried, yielding 10 parts of α-(4-amino-2-chlorophenyl)-4-chloro-α-methylbenzeneacetonitrile; mp. 135.2°C (intermediate 24).

In a similar manner there was also prepared:

α-(4-amino-2-chlorophenyl)-4-fluor -α-methylbenzeneacetonitrile; mp. 121.2°C (intermediate 25).

Example 6

A mixture of 31.1 parts of 4-chl ro-α-(2-chloro-4-nitr phenyl)-α-methyl-3-(trifluor - methyl)benzeneacetonitrile, 2 parts of a s lution of thiophene in methanol 4% and 480 parts of methanol was hydrogenated in the Parr apparatus at 50°C with 3 parts of platinum-on-charc al catalyst 5%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off, washed with tetrahydrofuran and the filtrate was evaporated in vacuo. The residue was crystallized from 160 parts of 2-propanol. The product was filtered off, washed with 2,2'-oxybispropane and dried, yielding 23.7 parts (82.4%) of (4-amino-2-chloro-α-[4-chloro-3-(trifluoromethyl)phenyl]-α-methylbenzeneacetonitrile; mp. 180.4°C (intermediate 26).

In a similar manner there was also prepared:
4-amino-α-(4-chlorophenyl)-α-methyl-2-(trifluoromethyl)benzeneacetonitrile (intermediate 27);
4-amino-2-chloro-α,α-bis(4-chlorophenyl)benzeneacetonitrile (intermediate 28);
4-amino-2-chloro-α-(4-chlorophenyl)-α-propylbenzeneacetonitrile (intermediate (29);
4-amino-α-butyl-2-chloro-α-(4-chlorophenyl)benzeneacetonitrile (intermediate 30);
4-amino-2,6-dichloro-α-(4-chlorophenyl)-α-methylbenzeneacetonitrile (intermediate 31);
4-amino-2-chloro-α-(4-chlorophenyl)-α,6-dimethylbenzeneacetonitrile (intermediate 32);
4-amino-2-chloro-α-(4-chlorophenyl)-α,5-dimethylbenzeneacetonitrile (intermediate 33);
4-amino-2-fluoro-α-(4-fluorophenyl)-α-methylbenzeneacetonitrile (intermediate 34);
4-amino-2,6-dichloro-α-(4-fluorophenyl)benzeneacetonitrile (intermediate 35);
4-amino-2-chloro-α-(4-fluorophenyl)-6-methylbenzeneacetonitrile (intermediate 36);
4-amino-α-(4-fluorophenyl)-2,6-dimethylbenzeneacetonitrile (intermediate 37);
4-amino-α-(4-chlorophenyl)-2,6-dimethylbenzeneacetonitrile (intermediate 38);.
Following the same procedures and using the appropriate starting materials there are also prepared:
4-amino-2-chloro-α-(4-chlorophenyl)benzeneacetonitrile (intermediate 39);
4-amino-2,6-dichloro-α-(4-chlorophenyl)benzeneacetonitrile (intermediate 40);
4-amino-2-chloro-α-(4-chlorophenyl)-6-methylbenzeneacetonitrile (intermediate 41);
4-amino-2-chloro-α-(4-fluorophenyl)benzeneaceonitrile (intermediate 42); and
4-amino-2-chloro-α-(4-methylphenyl)benzeneacetonitrile (intermediate 43).

Example 7

To a stirred and cooled (5—10°C) mixture of 15.2 parts of 4-amino-2-chloro-α-(4-chlorophenyl)-α,5-dimethylbenzeneacetonitrile, 14.4 parts of concentrate hydrochloric acid and 125 parts of acetic acid was added dropwise, during a 30 minutes period, a solution of 3.5 parts of sodium nitrite in 15 parts of water at about 10°C. Upon completion, the whole was stirred for 30 minutes and then 10 parts of sodium acetate and 7.8 parts of ethyl (2-cyanoacetyl)carbamate were added, during a period of 2 hours, at room temperature. The reaction mixture was poured into 500 parts of water. The product was filtered off, washed with water and dissolved in dichloromethane. The organic layer was dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of triochloromethane and methanol (95:5 by volume) as eluent. The pure fractions were collected and the eluent was evaporated in vacuo. The residue was stirred in 2-propanol. The product was filtered off, washed with 2,2'-oxybispropane and dried, yielding 17.5 parts (74.1%) of ethyl [2-[[5-chloro-4-[1-(4-chlorophenyl)-1-cyanoethyl]-2-methylphenyl]-hydrazono]-2-cyanoacetyl]carbamate (intermediate 44).

Following the same procedure and using equivalent amounts of the appropriate starting materials, there were also prepared:
ethyl [2-cyano-2-[[4-(1-cyano-1-phenylethyl)phenyl]hydrazono]-acetyl]carbamate (intermediate 45);
ethyl [2-[[3-chloro-4-[1-(4-chlorophenyl)-1-cyanoethyl]phenyl]hydrazono]-2-cyanoacetyl]carbamate (intermediate 46);
ethyl [2-[2-[3-chloro-4-[1-cyano-1-(4-fluorophenyl)ethyl]phenyl]-hydrazono]-2-cyanoacetyl]carbamate (intermediate 47);
ethyl [2-[[4-[1-(4-chlorophenyl)-1-cyanoethyl]-3-(trifluoromethyl)-phenyl]hydrazono]-2-cyanoacetyl]-carbamate (intermediate 48);
ethyl [2-[[4-[bis(4-chlorophenyl)cyanomethyl]-3-chlorophenyl]-hydrazono]-2-cyanoacetyl]carbamate (intermediate 49);
ethyl [2-[[3-chloro-4-[1-(4-chlorophenyl)-1-cyanobutyl]phenyl]hydrazono]-2-cyanoacetyl]carbamate (intermediate 50);
ethyl [2-[[3-chloro-4-[1-(4-chlorophenyl)-1-cyanopentyl]phenyl]hydrazono]-2-cyanoacetyl]carbamate (intermediate 51);
ethyl [2-[[3-chloro-4-[1-[4-chloro-3-(trifluoromethyl)phenyl]-1-cyanoethyl]phenyl]hydrazono]-2-cyano-acetyl]carbamate (intermediate 52);
ethyl [2-[2-[4-[1-(4-chlorophenyl)-1-cyanoethyl]-3,5-dichlorophenyl]hydrazono]-2-cyanoacetyl]carbamate (intermediate 53);
ethyl [2-[[3-chloro-4-[1-(4-chlorophenyl)-1-cyanoethyl]-5-methylphenyl]hydrazono]-2-cyanoacetyl]-carbamate (intermediate 54);
ethyl [2-cyano-2-[[4-[1-cyano-1-(4-fluorophenyl)ethyl]-3-fluorophenyl]hydrazono]-2-cyanoacetyl]-carbamate (int rmediat 55);

ethyl [2-[[3,5-dichloro-4-[cyano(4-flu rophenyl)methyl]phenyl]hydraz no]-2-cyanoacetyl]carbamat (intermediate 56);

thyl [2-[[3-chlor -4-[cyano(4-fluorophenyl)methyl]-5-methylphenyl]-hydrazon ]-2-cyanoacetyl]-carbamate; (intermediate 57)

ethyl [2-cyano-2-[[4-[cyano(4-fluorophenyl)methyl]-3,5-dimethylphenyl]hydrazono]acetyl]carbamate [intermediate 58);

ethyl [2-[[4-[(4-chlorophenyl)cyanomethyl]-3,5-dimethylphenyl]-hydrazono]-2-cyanoacetyl]carbamate (intermediate 59).

Following the same procedure and using the appropriate starting materials there are also prepared:

ethyl [2-[[3-chloro-4-[(4-chlorophenyl)cyanomethyl]phenyl]hydrazono]-2-cyanoacetyl]carbamate (intermediaate 60);

ethyl [2-[[3,5-dichloro-4-[(4-chlorophenyl)cyanomethyl]phenyl]hydrazono]-2-cyanoacetyl]carbamate (intermediate 61);

ethyl [2-[[3-chloro-4-[(4-chlorophenyl)cyanomethyl]-5-methylphenyl]hydrazono]-2-cyanoacetyl]-carbamate (intermediate 62);

ethyl [2-[[3-chloro-4-[(4-fluorophenyl)cyanomethyl]phenyl]hydrazono]-2-cyanoacetyl]carbamate (intermediate 63); and

ethyl [2-[[3-chloro-4-[(4-methylphenyl)cyanomethyl]phenyl]hydrazono]-2-cyanoacetyl]carbamate (intermediate 64).

## Example 8

A mixture of 7.8 parts of ethyl [2-cyano-2-[[4-(1-cyano-1-phenylethyl)phenyl]hydrazono]acetyl]-carbamate, 1.98 parts of anhydrous potassium acetate and 120 parts of acetic acid was stirred and refluxed for 3 hours. The reaction mixture was concentrated to a volume of 30 parts. Water was added till the product was precipitated. It was sucked off, washed with water and dissolved in trichloromethane. The remaining water was separated and the organic phase was dried, filtered and evaporated, yielding 6.86 parts of 2-[4-(1-cyano-1-phenylethyl)phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carbonitrile as a residue (intermediate 65).

In a similar manner there was also prepared:

2-[3-chloro-4-[1-(4-chlorophenyl)-1-cyanoethyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carbonitrile (intermediate 66):

2-(3-chloro-4-[1-cyano-1-(4-fluorophenyl)ethyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carbonitrile (intermediate 67);

2-[4-[1-(4-chlorophenyl)-1-cyanoethyl]-3-(trifluoromethyl)phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carbonitrile (intermediate 68);

2-[4-[bis(4-chlorophenyl)cyanomethyl]-3-chlorophenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carbonitrile (intermediate 69);

2-[3-chloro-4-[1-(4-chlorophenyl)-1-cyanobutyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carbonitrile (intermediate 70);

2-[3-chloro-4-[1-(4-chlorophenyl)-1-cyanopentyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carbonitrile (intermediate 71);

2-[3-chloro-4-[1-[4-chloro-3-(trifluoromethyl)phenyl]-1-cyanoethyl]phenyl-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carbonitrile (intermediate 72);

2-[4-[1-(4-chlorophenyl)-1-cyanoethyl]-3,5-dichlorophenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carbonitrile (intermediate 73);

2-[3-chloro-4-[1-(4-chlorophenyl)-1-cyanoethyl]-5-methylphenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carbonitrile (intermediate 74);

2-[5-chloro-4-[1-(4-chlorophenyl)-1-cyanoethyl]-2-methylphenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carbonitrile (intermediate 75);

2-[4-[1-cyano-1-(4-fluorophenyl)ethyl]-3-fluorophenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carbonitrile (intermediate 76);

2-[3,5-dichloro-4-[cyano(4-fluorophenyl)methyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carbonitrile (intermediate 77);

2-[3-chloro-4-[cyano[4-fluorophenyl)methyl]-5-methylphenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carbonitrile (intermediate 78);

2-[4-[cyano(4-fluorophenyl)methyl]-3,5-dimethylphenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carbonitrile (intermediate 79); and

2-[4-[(4-chlorophenyl)cyanomethyl]-3,5-dimethylphenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carbonitrile (intermediate 80).

Following the same procedure and using the appropriate starting materials there are also prepared:

2-[3-chloro-4-[(4-chlorophenyl)cyanomethyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carbonitrile (intermediate 81);

2-[3,5-dichloro-4-[(4-chlorophenyl)cyanomethyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carbonitrile (intermediate 82);

2-[3-chlor -4-[(4-chlorophenyl)cyanomethyl]-5-methylphenyl]-2,3,4,5-t trahydro-3,5-dioxo-1,2,4-triazine-6-carbonitrile (int rmediate 83);

2-[3-chloro-4-[(4-fluorophenyl)cyanomethyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carbonitrile (intermediate 84); and

2-[3-chloro-4-[(4-methylphenyl)cyanomethyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carb nitrile (intermediate 85).

Example 9

A mixture of 6.86 parts of 2-[4-(1-cyano-1-phenylethyl)phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carbonitrile, 30 parts of concentrate hydrochloric acid and 150 parts of acetic acid was stirred and refluxed for 24 hours. The reaction mixture was evaporated and the residue was dissolved in trichloromethane. The latter was dried, filtered and evaporated, yielding 7.2 parts of 2-[4-(1-cyano-1-phenylethyl)phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (intermediate 86).

In a similar manner there was also prepared:

2-[3-chloro-4-[1-(4-chlorophenyl)-1-cyanoethyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (intermediate 87);

2-[3-chloro-4-[1-cyano-1-(4-fluorophenyl)ethyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (intermediate 88);

2-[4-[1-(4-chlorophenyl)-1-cyanoethyl]-3-(trifluoromethyl)phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (intermediate 89);

2-[4-[bis(4-chlorophenyl)cyanomethyl]-3-chlorophenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (intermediate 90);

2-[3-chloro-4-[1-(4-chlorophenyl)-1-cyanobutyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (intermediate 91);

2-[3-chloro-4-[1-(4-chlorophenyl)-1-cyanopentyl]pentyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (intermediate 92);

2-[3-chloro-4-[1-[4-chloro-3-(trifluoromethyl)phenyl]-1-cyanoethyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (intermediate 93);

2-[4-(1-(4-chlorophenyl)-1-cyanoethyl]-3,5-dichlorophenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (intermediate 94);

2-[3-chloro-4-[1-(4-chlorophenyl)-1-cyanoethyl]-5-methylphenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (intermediate 95);

2-[5-chloro-4-[1-(4-chlorophenyl)-1-cyanoethyl]-2-methylphenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (intermediate 96);

2-[4-[1-cyano-1-(4-fluorophenyl)ethyl]-3-fluorophenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (intermediate 97);

2-[3,5-dichloro-4-[cyano(4-fluorophenyl)methyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (intermediate 98);

2-[3-chloro-4-[cyano(4-fluorophenyl)methyl]-5-methylphenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (intermediate 99);

2-[4-[cyano(4-fluorophenyl)methyl]-3,5-dimethylphenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (intermediate 100); and

2-[4-[(4-chlorophenyl)cyanomethyl]-3,5-dimethylphenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (intermediate 101).

Following the same procedure and using the appropriate starting materials there are also prepared:

2-[3-chloro-4-[(4-chlorophenyl)cyanomethyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (intermediate 102);

2-[3,5-dichloro-4-[(4-chlorophenyl)cyanomethyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (intermediate 103);

2-[3-chloro-4-[(4-chlorophenyl)cyanomethyl]-5-methylphenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (intermediate 104);

2-[3-chloro-4-[(4-fluorophenyl)cyanomethyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (intermediate 105); and

2-[3-chloro-4-[(4-methylphenyl)cyanomethyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (intermediate 106).

Example 10

To a stirred mixture of 16 parts of 2-[3-chloro-4-[(4-chlorophenyl)-hydroxymethyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione and 150 parts of trichloromethane were added dropwise, during a period of 5 minutes, 16 parts of thionyl chloride. Upon completion, stirring was continued for 3 hours at reflux temperature. The reaction mixture was evaporated in vacuo. Methylbenzene was added and the whole was evaporated again, yielding 14 parts (83.1%) of 2-[3-chloro-4-[chloro(4-chlorophenyl)methyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione as a residue (intermediate 107).

In a similar manner there were also prepared:

2-[4-[chloro[4-chlorophenyl)methyl]-3,5-dichlorophenyl]-1,2,4-triazine-3,5-(2*H*,4*H*)-dione (intermediate 108);

2-[3-chloro-4-[chloro(4-chloroph nyl)methyl]-5-methylphenyl]-1,2,4-triazine-3,5-(2*H*,4*H*)-dione (intermediate 109);

2-[3-chloro-4-[chloro(4-fluorophenyl)methyl]phenyl]-1,2,4-triazine-3,5-(2*H*,4*H*)-di ne (intermediate 110); and

2-[3-chl ro-4-[chlor (4-methylphenyl)methyl]phenyl]-1,2,4-triazine-3,5-(2*H*,4*H*)-dione (interm diate 111).

Following the sam procedur and using the appropriate starting materials there are also prepared:

2-[3-chloro-4-[1-chloro-1-(4-chlorophenyl)ethyl)-5-methylphenyl]-1,2,4-triazine-3,5-[2*H*,4*H*]-dione; (intermediate 112)

2-[4-(1-chloro-1-phenylethyl)phenyl]-1,2,4-triazine-3,5-[2*H*,4*H*]-dione; (intermediate 113);

2-[3-chloro-4-[1-chloro-1-(4-chlorophenyl)ethyl]phenyl]-1,2,4-triazine-3,5-[2*H*,4*H*]-dione; (intermediate 114);

2-[3-chloro-4-[1-chloro-1-(4-fluorophenyl)ethyl]phenyl]-1,2,4-triazine-3,5-[2*H*,4*H*]-dione; (intermediate 115);

2-[4-[1-chloro-1-(4-chlorophenyl)ethyl]-3-(trifluoromethyl)phenyl]-1,2,4-triazine-3,5-[2*H*,4*H*]-dione; (intermediate 116);

2-[4-[bis(4-fluorophenyl)chloromethyl]-3-(trifluoromethyl)phenyl]-1,2,4-triazine-3,5-[2*H*,4*H*]-dione; (intermediate 117);

2-[3-chloro-4-[1-chloro-1-(4-chlorophenyl)butyl]phenyl]-1,2,4-triazine-3,5-[2*H*,4*H*]-dione; (intermediate 118);

2-[3-chloro-4-[1-chloro-1-(4-chlorophenyl)pentyl]phenyl]-1,2,4-triazine-3,5-[2*H*,4*H*]-dione; (intermediate 119);

2-[3-chloro-4-[1-chloro-1-[4-chloro-3-trifluoromethyl)phenyl]ethyl]phenyl]-1,2,4-triazine-3,5-[2*H*,4*H*]-dione; (intermediate 120);

2-[3,5-dichloro-4-[1-chloro-1-(4-chlorophenyl)ethyl]phenyl]-1,2,4-triazine-3,5-[2*H*,4*H*]-dione; (intermediate 121);

2-[5-chloro-4-[1-chloro-1-(4-chlorophenyl)ethyl]-2-methylphenyl]-1,2,4-triazine-3,5-[2*H*,4*H*]-dione; (intermediate 122);

2-[4-[1-chloro-1-(4-fluorophenyl)ethyl]-3-fluorophenyl]-1,2,4-triazine-3,5-[2*H*,4*H*]-dione; (intermediate 123);

2-[3,5-dichloro-4-[chloro(4-fluorophenyl)methyl]phenyl]-1,2,4-triazine-3,5-[2*H*,4*H*]-dione; (intermediate 124);

2-[3-chloro-4-[chloro(4-fluorophenyl)methyl]-5-methylphenyl]-1,2,4-triazine-3,5-[2*H*,4*H*]-dione; (intermediate 125);

2-[4-[chloro(4-fluorophenyl)methyl]-3,5-dimethylphenyl]-1,2,4-triazine-3,5-[2*H*,4*H*]-dione; (intermediate 126);

2-[4-[chloro(4-chlorophenyl)methyl]-3,5-dimethylphenyl]-1,2,4-triazine-3,5-[2*H*,4*H*]-dione; (intermediate 127).

B) Preparation of Final compounds

Example 11

A mixture of 11.1 parts of 2-[3-chloro-4-[1-[4-chlorophenyl)-1-cyanoethyl]-5-methylphenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid and 15 parts of 2-mercaptoacetic acid was stirred and heated for 2 hours at 180°C. The reaction mixture was cooled, water was added and the whole was treated with sodium hydrogen carbonate. The product was extracted with trichloromethane. The organic layer was dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol (95:5 by volume) as eluent. The pure fractions were collected and the eluent was evaporated in vacuo. The residue was stirred in 2,2'-oxybispropane. The product was filtered off and dried, yielding 5 parts (50%) of 2-chloro-α-(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)-α,6-dimethylbenzeneacetonitrile; mp. 226.7°C (compound 1).

In a similar manner there were also prepared:

4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)-α-methyl-α-phenyl-benzeneacetonitrile; mp. 189.2°C (compound 2);

2-chloro-α-(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)-α-methylbenzeneacetonitrile; mp. 235.1°C (compound 3);

2-chloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)-α-(4-fluorophenyl)-α-methylbenzeneacetonitrile; mp. 202.8°C (compound 4);

α-(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)-α-methyl-2-(trifluoromethyl)benzeneacetonitrile; mp. 232.8°C (compound 5);

α,α-bis(4-chlorophenyl)-2-chloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)benzeneacetonitrile; mp. 229.9°C (compound 6);

2-chloro-α-(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3)-yl)-α-propylbenzeneacetonitrile; mp. 124.2°C (compound 7)

α-butyl-2-chloro-α-(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)benzeneacetonitrile; mp. 126.3°C; (compound 8)

4-chloro-α-[2-chl r -4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)phenyl]-α-methyl-3-(trifluoromethyl)benzeneac tonitrile; mp. 233.7°C; (comp und 9)

2,6-dichloro-α-(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)-α-methylbenzeneacetonitrile; mp. 184.5°C (compound 10); and

2-chloro-α-(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)-α,5-dimethylbenzeneacetonitrile; mp. 285.8°C (compound 11).

In a similar manner there were also prepared:

4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)-2-fluoro-α-(4-fluorophenyl)-α-methylbenzeneacetonitrile; mp. 211.6°C (compound 12);

2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)-α-(4-fluorophenyl)benzeneacetonitrile; mp. 250.2°C (compound 13);

2-chloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)-α-(4-fluorophenyl)-6-methylbenzeneacetonitrile; mp. 222.8°C (compound 14);

4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)-α-(4-fluorophenyl)-2,6-dimethylbenzeneacetonitrile; mp. 272.3°C (compound 15); and

α-(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)-2,6-dimethylbenzeneacetonitrile; mp. 259.6°C (compound 16).

Example 12

A mixture of 12 parts of 2-[3-chloro-4-[chloro(4-chlorophenyl)methyl]phenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione and 5.4 parts of copper cyanide was stirred and heated first for 3 hours at 130°C and for 3 hours at 180°C. After cooling, the precipitated product was dissolved in a mixture of trichloromethane and methanol (90:10 by volume). The inorganic precipitate was filtered off and the filtrate was evaporated in vacuo. The residue was purified four times by column chromatography over silica gel using first a mixture of trichloromethane and acetonitrile (90:10 by volume), second a mixture of tetrachloromethane and methanol (93:7 by volume) and then twice a mixture of tetrachloromethane and acetonitrile (95:5 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was further purified by column chromatography (HPLC) over silica gel using a mixture of triochloromethane and methanol (98:2 by volume) as eluent. The pure fractions were collected and the eluent was evaporated in vacuo. The residue was dried, yielding 1.3 parts (11.2%) of 2-chloro-α-(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)benzeneacetonitrile; mp. 196.8°C (compound 17).

In a similar manner there were also prepared:

2,6-dichloro-α-(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)benzeneacetonitrile; mp. 290.5°C (compound 18);

2-chloro-α-(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)-6-methylbenzeneacetonitrile; mp. 267.2°C (compound 19);

2-chloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)-α-(4-fluorophenyl)benzeneacetonitrile; mp. 185.2°C (compound 20); and

2-chloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)-α-(4-methylphenyl)benzeneacetonitrile; mp. 162.3°C (compound 21).

C) Pharmacological Examples

The strong anti-protozoal activity of the compounds of formula (I), the pharmaceutically acceptable acid addition salts and the possible stereochemically isomeric forms thereof is clearly evidenced by the data obtained in the following experiments, which data are only given to illustrate the useful anti-protozoal properties of all the compounds embraced within the invention and not to limit the invention either with respect to the scope of susceptible *Protozoa* nor with respect to the scope of formula (I).

Example 13

Outline of anaticoccidial efficacy test against *Eimeria tenella*.

Hisex chickens were fed with a commercial basal ration not containing a coccidiostatic agent.

Eighteen-day-old chickens were sorted in groups of two birds. Water was supplied automatically and medicated feed was supplied ad libitum from the day of infection (day 0) until the seventh day (not included) after infection. Unmedicated feed was supplied ad libitum to two groups of four birds for uninfected and infected controls.

Unmedicated feed was a commercial basal ration not containing a coccidiostatic agent. Medicated feed was prepared from unmedicated feed by thoroughly mixing the latter with an amount of the tested compound.

On day 0 the birds were inoculated orally with $10^5$ sporulated oocysts of *Eimeria tenella*. On day 5 the faecal score was determined and graded:

0 = no blood spots
1 = one or two blood spots
2 = three to five blood spots
3 = more than five blood spots

On the seventh day oocyst production is determined by collecting the feces and the oocyst c unt per gram feces (OPG) and the birds are weighed.

In Table 1 the first column shows the average relative weight gain in percent c mpared with the non-infected controls. The second column shows the average faecal score and the third column illustrates the average ocyst c unt.

Table 1

| Comp. No. | dose of tested compound in ppm in feed | average relative weight gain | average faecal score | average oocyst count (OPG) x 1000 |
|---|---|---|---|---|
| 1 | 100 | 92 | 0 | 0 |
| | 10 | 99 | 0 | 0 |
| | 5 | 96 | 0 | 0 |
| 2 | 100 | 93 | 0 | 0 |
| 3 | 100 | 94 | 0 | 0 |
| | 10 | 92 | 0 | 0 |
| 4 | 100 | 103 | 0 | 0 |
| | 10 | 100 | 0 | 0 |
| | 5 | 92 | 1.0 | 0 |
| 5 | 100 | 94 | 0 | 0 |
| | 10 | 92 | 0.8 | 0 |
| 6 | 100 | 98 | 0 | 0 |
| | 10 | 97 | 1.5 | 0 |
| 10 | 10 | 97 | 0 | 0 |
| | 5 | 98 | 0 | 0 |
| | 1 | 94 | 0.5 | 0 |
| * | - | 100 | 0 | 0 |
| ** | - | 78 | 2.9 | 459 |
| 13 | 1 | 101 | 0 | 0 |
| | 0.5 | 96 | 0 | 0 |

TABLE 1 (continued)

| Comp. No. | dose of tested ccmpound in ppm in feed | average relative weight gain | average faecal score | average oocyst count (OPG) x 1000 |
|---|---|---|---|---|
| 14 | 1 | 98 | 0 | 0 |
| 15 | 100 | 99 | 0 | 0 |
| | 10 | 99 | 0 | 0 |
| 16 | 100 | 94 | 0 | 0 |
| | 10 | 97 | 0 | 0 |
| | 5 | 94 | 0 | 0 |
| 17 | 100 | 98 | 0 | 0 |
| | 10 | 102 | 0 | 0 |
| | 5 | 100 | 0 | 0 |
| | 1 | 98 | 1.0 | 0 |
| | 0.5 | 97 | 0.5 | 0 |
| 18 | 100 | 98 | 0 | 0 |
| | 10 | 101 | 0 | 0 |
| | 5 | 98 | 0 | 0 |
| | 1 | 102 | 0 | 0 |
| | 0.5 | 97 | 0.1 | 0 |
| 19 | 100 | 99 | 0 | 0 |
| | 10 | 108 | 0 | 0 |
| | 5 | 99 | 0 | 0 |
| | 1 | 99 | 0 | 0 |
| | 0.5 | 94 | 0.4 | 0 |
| 20 | 100 | 95 | 0 | 0 |
| | 10 | 99 | 0 | 0 |
| | 5 | 100 | 0 | 0 |
| | 1 | 94 | 0.2 | 0 |
| 21 | 100 | 92 | 0 | 0 |
| | 10 | 95 | 0.5 | 0 |

* = non-infected control

** = infected control

Example 14

Outline of anticoccidial efficacy test against *Eimeria acervulina.*

Hisex chickens wer fed with a commercial basal ration not containing a coccidiostatic agent.

Eighteen-day-old chickens were sorted in gr ups of four birds. Water was supplied automatically and medicated feed was supplied ad libitum fr m the day of infection (day 0) until the seventh day (not included) after infection. Unmedicated feed was supplied ad libitum to two groups of four birds for uninfected and infected controls.

Unmedicated feed was a commercial basal ration not containing a coccidiostatic agent. Medicated feed was prepared from unmedicated feed by thoroughly mixing the latter with an amount of the tested compound.

On day 0 the birds were inoculated orally with $2.10^6$ sporulated oocysts of *Eimeria acervulina.* On day 4 and 5 the faecal score was determined and graded:

0 = normal
1 = slightly soft faeces
2 = white watery diarrhea
3 = slimy mucoid diarrhea

On the fifth and sixth day oocyst production is determined by collecting the feces and the oocyst count per gram feces (OPG) and the birds are weighed.

In table 2 the first column shows the average relative weight gain in percent compared with the non-infected controls. The second column shows the average faecal score and the third column illustrates the average oocyst count.

Tabl 2

| Comp. No. | dose of tested ccmpound in ppm in feed | average relative weight gain | average faecal score | average oocyst count (OPG) x 1000 |
|---|---|---|---|---|
| 1 | 100 | 81 | 0.4 | 0 |
| * | - | 100 | 0 | 0 |
| ** | - | 73 | 2.8 | 356 |
| 3 | 100 | 98 | 0 | 0 |
| | 10 | 84 | 1.1 | 147 |
| 4 | 100 | 97 | 0 | 0 |
| | 10 | 86 | 1.1 | 35 |
| | 5 | 92 | 1.0 | 0 |
| 5 | 100 | 94 | 0 | 0 |
| 6 | 100 | 91 | 0 | 3 |
| 10 | 100 | 85 | 0.2 | 0 |
| | 10 | 85 | 0.3 | 14 |
| | 5 | 90 | 1.2 | 33 |
| 12 | 100 | 97 | 0.3 | 0 |
| 13 | 100 | 97 | 0 | 0 |
| | 10 | 97 | 0.3 | 28 |
| | 5 | 94 | 0.3 | 14 |
| | 1 | 93 | 0.3 | 55 |
| 14 | 100 | 99 | 0 | 0 |
| | 10 | 102 | 0 | 5 |
| 15 | 100 | 99 | 0 | 0 |
| | 10 | 95 | 0.5 | 44 |
| 16 | 100 | 94 | 0 | 0 |
| | 10 | 91 | 0.1 | 20 |
| 22 | 100 | 94 | 0 | 0 |
| | 10 | 91 | 0.2 | 11 |
| | 5 | 101 | 0 | 23 |
| 23 | 100 | 99 | 0 | 0 |
| | 10 | 99 | 0 | 0 |
| | 5 | 102 | 0 | 6 |

TABLE 2 (continued)

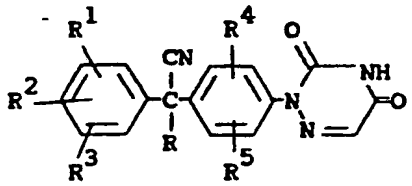
| Comp. No. | dose of tested compound in ppm in feed | average relative weight gain | average faecal score | average oocyst count (OPG) x 1000 |
|---|---|---|---|---|
| | 1 | 100 | 0 | 29 |
| | 0.5 | 90 | 0.7 | 17 |
| 24 | 100 | 98 | 0 | 0 |
| | 10 | 92 | 0 | 10 |
| | 5 | 96 | 0 | 0 |
| | 1 | 92 | 0.5 | 44 |
| 25 | 100 | 98 | 0 | 0 |
| | 10 | 97 | 0.1 | 36 |

* = non-infected control

** = infected control

**Claims**

1. A chemical compound having the formula



(I)

a pharmaceutically acceptable acid addition salt or a possible stereo-chemically isomeric form thereof, wherein:

$R^1$, $R^2$ and $R^3$ are each independently hydrogen, halo, trifluoromethyl, $C_{1-6}$ alkyl, $C_{1-6}$ alkyloxy, $C_{1-6}$ alkylthio or $C_{1-6}$ alkylsulfonyl;

$R^4$ and $R^5$ are each independently hydrogen, halo, trifluoromethyl or $C_{1-6}$ alkyl; and

R is hydrogen, $C_{1-6}$ alkyl, cyclo $C_{3-6}$ alkyl or phenyl optionally substituted with up to three substituents each independently selected from the group consisting of halo, trifluoromethyl, $C_{1-6}$ alkyl, $C_{1-6}$ alkyloxy; $C_{1-6}$ alkylthio and $C_{1-6}$ alkylsulfonyloxy.

2. A chemical compound according to claim 1, wherein $R^1$ and $R^2$ are, each indpendently, hydrogen, halo, trifluoromethyl, or $C_{1-6}$ alkyl; $R^3$ is hydrogen; R is hydrogen, $C_{1-6}$ alkyl, phenyl or halophenyl; $R^4$ and $R^5$ are, each independently, hydrogen, halo, trifluoromethyl or $C_{1-6}$ alkyl.

3. A chemical compound according to claim 2, wherein $R^1$ is halo; $R^2$ and $R^3$ are both hydrogen; R is hydrogen, $C_{1-6}$ alkyl or halophenyl.

4. A chemical compound according to claim 3, wherein $R^1$ is 4-halo; R is hydrogen or methyl; and $R^4$ and $R^5$ are, each independently, hydrogen, halo, methyl or trifluoromethyl, said $R^4$ and $R^5$ being substituted on the 2 and 6 position of the phenyl moiety bearing said $R^4$ and $R^5$.

5. A chemical compound according to claim 1 wherein the compound is 2-chloro-α-(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)benzeneacetonitrile.

6. A chemical compound according to claim 1 wherein the compound is 2,6-dichloro-α-(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)benzeneacetonitrile.

7. A chemical compound according to any one of claims 1 to 6 for use as a medicine.

8. A chemical compound according to any one of claims 1 to 6 for use as an anti-protozoal medicine.

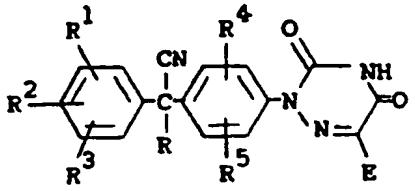
9. A pharmaceuticaal composition comprising an inert carrier and as an active ingredi nt a pharmaceuticaly acceptable amount f a comp und according to any one of claims 1 t 6.

10. A pharmaceutical compositi n according t claim 9 for use as an anti-protozoal m dicine.

11. A process of preparing a pharmaceutical composition characterized in that a therapeutically eff ctive am unt f a compound as claimed in any ne f claims 1 to 6 is intimately mixed with a suitable pharmaceutical carrier.

12. A process of preparing a chemical compound as claimed in any one of claims 1 to 6, characterized by

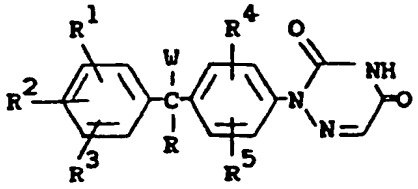
i) eliminating the group E of an intermediate triazadione having the formula



(III)

wherein E represents an electron attracting group, said elimination being carried out at higher temperatures, if desired, in the presence of an acid, said acid being optionally used as a solvent and optionally, if further desired, in the presence of a reaction-inert solvent; or

ii) reacting an intermediate of formula

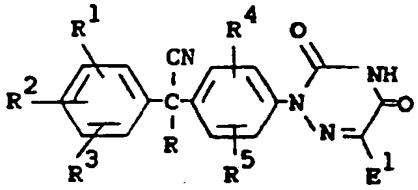


(VI)

wherein W represents a reactive leaving group, with a cyanide, if desired, in the presence of a reaction-inert solvent.

13. A process according to claim 12, wherein E is a carboxyl group; and W is halo, methylsulfonyloxy or 4-methylphenylsulfonyloxy.

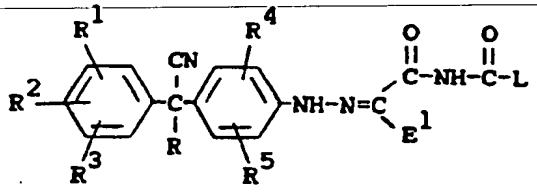
14. A process according to claim 13, wherein the intermediate (III) wherein E stands for carboxyl is produced by hydrolizing an intermediate of formula



(III-a)

wherein $E^1$ is cyano, $C_{1-6}$ alkyloxycarbonyl, or amido.

15. A process according to claim 14, wherein the intermediate of formula (III-a) is produced by a cyclization reaction starting from an intermediate of formula



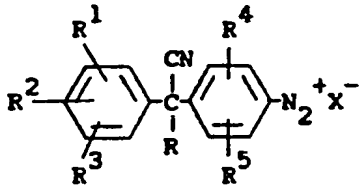
(II-a)

wherein L is a reactive leaving group.

16. A process according to claim 15, wherein L is $C_{1-6}$ alkyloxy or halo and wherein the cyclization reaction is conducted in an acidic medium.

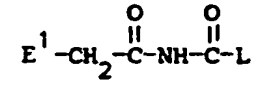
17. A process according to claim 16, wherein the acidic medium is acetic acid in the presence of an alkalimetal acetate.

18. A process acc rding to claim 15, wherein the intermediate of formula (II-a) is produced by reacting a diazonium of f rmula



(VII)

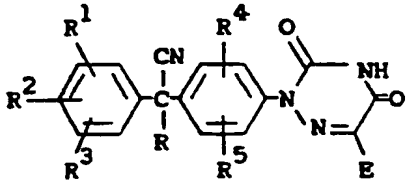
wherein $X^-$ is an anion arising from an acid, with an intermediate of formula



(VIII)

19. A process according to claim 18 wherein $X^-$ is a halide, L is $C_{1-6}$ alkyloxy and $E^1$ is cyano.

20. A chemical compound of formula

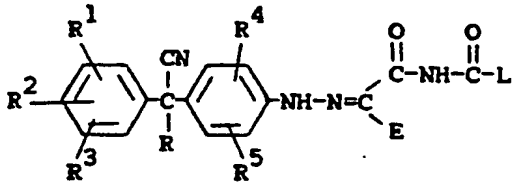


(III)

the acid addition salts and possible stereochemically isomeric forms thereof, wherein R, $R^1$, $R^2$, $R^3$, $R^4$, $R^5$ are as defined in Claim 1; and E is an electron attracting group selected from the group consisting of carboxyl, sulfonyloxy, sulfinyloxy, amido, cyano, $C_{1-6}$ alkylsulfonyl, phenylsulfonyloxy, $C_{1-6}$ alkylphenylsulfonyloxy, halophenylsulfonyloxy and $C_{1-6}$ alkyloxycarbonyl.

21. A chemical compound according to claim 20, wherein E is carboxyl, cyano, $C_{1-6}$ alkyloxycarbonyl or amido.

22. A chemical compound having the formula



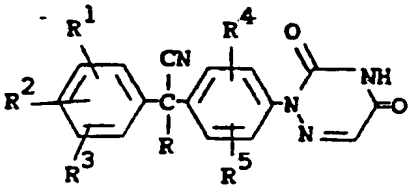
(II)

the acid addition salts and possible stereochemically isomeric forms thereof, wherein R, $R^1$, $R^2$, $R^3$, $R^4$ and $R^5$ are as defined in Claim 1; and E is an electron attracting group selected from the group consisting of carboxyl, sulfonyloxy, sulfinyloxy, amido, cyano, $C_{1-6}$ alkylsulfonyl, phenylsulfonyloxy, $C_{1-6}$ alkylphenylsulfonyloxy, halophenylsulfonyloxy and $C_{1-6}$ alkyloxycarbonyl.

23. A chemical compound according to claim 22, wherein E is carboxyl, cyano, $C_{1-6}$ alkyloxycarbonyl or amido.

**Patentansprüche**

1. Chemische Verbindung mit der Formel



(I)

ein pharmazeutisch annehmbares Säureadditionssalz der ein mögliche stereochemisch isomere Form hievon, worin:

$R^1$, $R^2$ und $R^3$ jeweils unabhängig voneinander Wasserst ff, Hal g n, Trifluormethyl, $C_{1-6}$Alkyl, $C_{1-6}$Alkyloxy, $C_{1-6}$Alkylthio d r $C_{1-6}$Alkylsulfonyl darstellen;

$R^4$ und $R^5$ jeweils unabhängig voneinander für Wasserstoff, Halogen, Trifluormethyl oder $C_{1-6}$Alkyl stehen; und

R Wasserstoff, $C_{1-6}$Alkyl, Cyclo $C_{3-6}$ alkyl oder Phenyl, gegebenenfalls substituiert mit bis zu 3 Substituenten, welche unabhängig voneinander aus der aus Halogen, Trifluormethyl, $C_{1-6}$Alkyl, $C_{1-6}$Alkyloxy, $C_{1-6}$Alkylthio und $C_{1-6}$Alkylsulfonyloxy bestehenden Gruppe ausgewählt sind, bedeuten.

2. Chemische Verbindung nach Anspruch 1, worin

$R^1$ und $R^2$ unabhängig voneinander Wasserstoff, Halogen, Trifluormethyl oder $C_{1-6}$Alkyl sind;

$R^3$ für Wasserstoff steht;

R Wasserstoff, $C_{1-6}$Alkyl, Phenyl oder Halogenphenyl bedeutet;

$R^4$ und $R^5$ jeweils unabhängig voneinander Wasserstoff, Halogen, Trifluormethyl oder $C_{1-6}$Alkyl sind.

3. Chemische Verbindung nach Anspruch 2, worin

$R^1$ Halogen ist;

$R^2$ und $R^3$ ist;

$R^2$ und $R^3$ beide für Wasserstoff stehen;

R Wasserstoff, $C_{1-6}$Alkyl oder Halogenphenyl bedeutet.

4. Chemische Verbindung nach Anspruch 3, worin

$R^1$ für 4-Halogen steht;

R Wasserstoff oder Methyl bedeutet; und

$R^4$ und $R^5$ jeweils unabhängig voneinander Wasserstoff, Halogen, Methyl oder Trifluormethyl darstellen, welches $R^4$ und $R^5$ an der 2- und 6-Stellung der die genannten $R^4$ und $R^5$ tragenden Phenylgruppen substituiert sind.

5. Chemische Verbindung nach Anspruch 1, worin die Verbindung 2-Chlor-alpha-(4-chlorphenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)benzolacetonitril ist.

6. Chemische Verbindung nach Anspruch 1, worin die Verbindung 2,6-Dichlor-alpha-(4-chlorphenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)benzolacetonitril ist.

7. Chemische Verbindung nach einem der Ansprüche 1 bis 6 zur Verwendung als ein Arzneimittel.

8. Chemische Verbindung nach einem der Ansprüche 1 bis 6 zur Verwendung als ein anti-Protozoen-Arzneimittel.

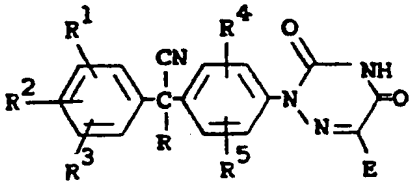
9. Pharmazeutische Zusammensetzung, umfassend einen inerten Träger und als einen wirksamenen Bestandteil eine pharmazeutisch annehmbare Menge einer Verbindung nach einem der Ansprüche 1 bis 6.

10. Pharmazeutische Zusammensetzung nach Anspruch 9 zur Verwendung als ein anti-Protozoen-Arzneimittel.

11. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, dadurch gekennzeichnet, daß eine therapeutisch wirksame Menge einer Verbindung nach einem der Ansprüche 1 bis 6 mit einem geeigneten pharmazeutischen Träger innig vermischt wird.

12. Verfahren zum Herstellen einer chemischen Verbindung nach einem der Ansprüche 1 bis 6, gekennzeichnet durch:

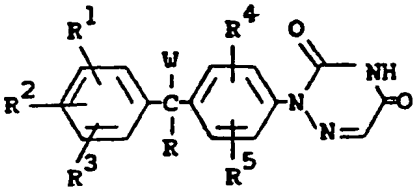
i) Eliminieren der Gruppe E einer Triazadion-Zwischenverbindung mit der Formel



(III)

worin E eine Elektronen-anziehende Gruppe darstellt, welche Eliminierung bei höheren Temperaturen, gewünschtenfalls in Gegenwart einer Säure, welche Säure wahlweise als ein Lösungsmittel verwendet wird, und wahlweise, wenn weiter gewünscht, in Gegenwart eines reaktionsinerten Lösungsmittels ausgeführt wird; oder

ii) Umsetzen einer Zwischenverbindung der Formel

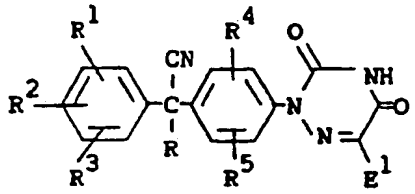


(VI)

worin W eine reaktive Leaving-Gruppe darstellt, mit einem Cyanid, gewünschtenfalls in Gegenwart eines reaktionsinerten Lösungsmittels.

13. Verfahren nach Anspruch 12, w rin E ein Carboxylgruppe darst llt; und W Hal gen, Methylsulfonyloxy oder 4-Methylphenylsulfonyloxy ist.

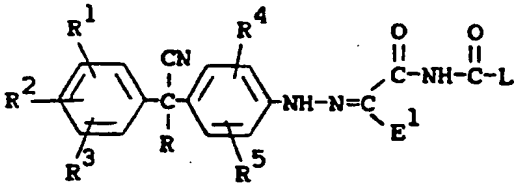
14. Verfahren nach Anspruch 13, worin die Zwischenverbindung (III), worin E für Carb xyl steht, durch Hydrolysieren einer Zwischenverbindung der Formel



(III-a)

hergestellt wird, worin $E^1$ für Cyano, $C_{1-6}$Alkyloxycarbonyl oder Amido steht.

15. Verfahren nach Anspruch 14, worin die Zwischenverbindung der Formel (III-a) durch eine Cyclisierungsreaktion, ausgehend von einer Zwischenverbindung der Formel



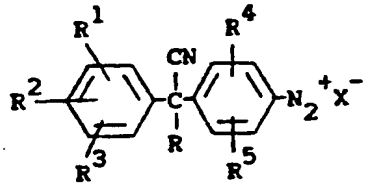
(II-a)

hergestellt wird, worin L eine reaktive Leaving-Gruppe darstellt.

16. Verfahren nach Anspruch 15, worin L für $C_{1-6}$Alkyloxy oder Halogen steht und worin die Cyclisierungsreaktion in einem sauren Medium durchgeführt wird.

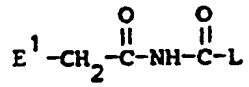
17. Verfahren nach Anspruch 16, worin das saure Medium Essigsäure in Gegenwart eines Alkalimetallacetats ist.

18. Verfahren nach Anspruch 15, worin die Zwischenverbindung der Formel (II-a) durch Umsetzen eines Diazoniums der Formel



(VII)

worin $X^-$ ein aus einer Säure entstehendes Anion ist, mit einer Zwischenverbindung der Formel

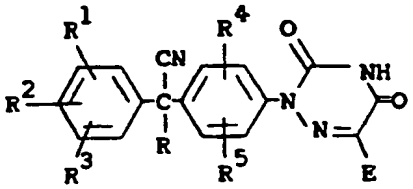


(VIII)

hergestellt wird.

19. Verfahren nach Anspruch 18, worin $X^-$ ein Halogenid ist, L für $C_{1-6}$Alkyloxy steht und $E^1$ Cyano darstellt.

20. Chemische Verbindung der Formel



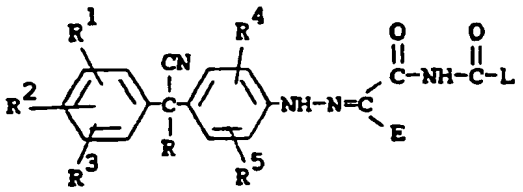
(III)

di Säureadditionssalze und die m"glich n stereochemisch isomeren Formen hievon, worin R, $R^1$, $R^2$, $R^3$, $R^4$, $R^5$ wie in Anspruch 1 definiert sind und E eine Elektronen-anziehende Gruppe, ausgewählt aus der aus

Carboxyl, Sulfonyloxy, Sulfinyloxy, Amido, Cyano, $C_{1-6}$Alkylsulfonyl, Phenylsulfonyloxy, $C_{1-6}$Alkylphenylsulfonyloxy, Halogenphenylsulfonyloxy und $C_{1-6}$Alkyloxycarbonyl bestehenden Gruppe, ist.

21. Chemische Verbindung nach Anspruch 20, worin E für Carboxyl, Cyan , $C_{1-6}$Alkyloxycarbonyl d r Amido steht.

22. Chemische Verbindung der Formel



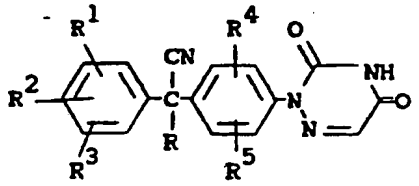
(II)

die Säureadditionssalze und möglichen stereochemisch isomeren Formen hievon, worin R, $R^1$, $R^2$, $R^3$, $R^4$ und $R^5$ wie in Anspruch 1 definiert sind; und E eine Elektronen-anziehende Gruppe, ausgewählt aus der aus Carboxyl, Sulfonyloxy, Sulfinyloxy, Amido, Cyano, $C_{1-6}$Alkylsulfonyl, Phenylsulfonyloxy, $C_{1-6}$Alkylphenylsulfonyloxy, Halogenphenylsulfonyloxy und $C_{1-6}$Alkyloxycarbonyl bestehenden Gruppe, ist.

23. Chemische Verbindung nach Anspruch 22, worin E für Carboxyl, Cyano, $C_{1-6}$Alkyloxycarbonyl oder Amido steht.

**Revendications**

1. Composé chimique de formule



(I)

sel d'addition d'acide pharmaceutiquement acceptable et forme stéréoisomère éventuelle de celui-ci, dans lequel:

$R^1$, $R^2$ et $R^3$ sont chacun, indépendamment, un hydrogène, un halogène, un groupe trifluorométhyle, alkyle en $C_1$—$C_6$, alkyloxy en $C_1$—$C_6$, alkylthio en $C_1$—$C_6$ ou alkylsulfonyle en $C_1$—$C_6$;

$R^4$ et $R^5$ sont chacun indépendamment un hydrogène, un halogène, un groupe trifluorométhyle ou alkyle en $C_1$—$C_6$; et

R est un hydrogène, un groupe alkyle en $C_1$—$C_6$, cycloalkyle en $C_3$—$C_6$ ou phényle éventuellement substitué par jusqu'à trois substituants choisis chacun indépendamment dans le groupe constitué par un halogène, un groupe trifluorométhyle, alkyle en $C_1$—$C_6$, alkyloxy en $C_1$—$C_6$, alkylthio en $C_1$—$C_6$ et alkylsulfonyloxy en $C_1$—$C_6$.

2. Composé chimique selon la revendication 1, dans lequel $R^1$ et $R^2$ sont chacun, indépendamment, un hydrogène, un halogène, un groupe trifluorométhyle ou alkyle en $C_1$—$C_6$; $R^3$ est un hydrogène, R est un hydrogène, un groupe alkyle en $C_1$—$C_6$, phényle, ou halogénophényle.

3. Composé chimique selon la revendication 2, dans lequel $R^1$ est un halgène; $R^2$ et $R^3$ sont tous deux des atomes d'hydrogène; R est un hydrogène, un groupe alkyle en $C_2$—$C_6$ ou halogénophényle.

4. Composé chimique selon la revendication 3, dans lequel $R^1$ est un halogène en position 4, R est un hydrogène ou un groupe méthyle et $R^4$ et $R^5$ sont chacun, indépendamment, un hydrogène, un halogène, un groupe méthyle ou trifluorométhyle, lesdits $R^4$ et $R^5$ étant substituants en position 2 et 6 du groupement phényle portant lesdits $R^4$ et $R^5$.

5. Composé chimique selon la revendication 1, dans lequel le composé est le 2-chloro-α-(4-chlorophényl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazine-2(3H)-yl)benzèneacétonitrile.

6. Composé chimique selon la revendication 1, dans lequel le composé est le 2,6-dichloro-α-(4-chlorophényl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazine-2(3H)-yl)benzèneacétonitrile.

7. Composé chimique selon l'une quelconque des revendications 1 à 6, utilisable comme médicament.

8. Composé chimique selon l'une quelconque des revendications 1 à 6, utilisable comme médicament antiprotozoaire.

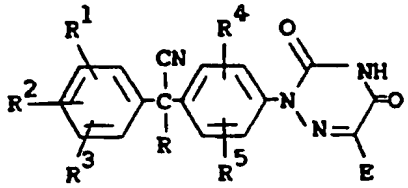
9. Composition pharmaceutique comprenant un véhicule inerte et, comme ingrédient actif, une quantité pharmaceutiquement acceptable d'un composé selon l'une quelconque des revendications 1 à 6.

10. Compositi n pharmaceutiqu selon la r vendication 9, utilisable comme médicament antiprotozoaire.

11. Procédé de préparation d'une compositi n pharmaceutique, caractérisé en ce que l'on mélange intimement une quantité thérapeutiquement efficace d'un comp sé selon l'une quelconque des revendications 1 à 6 avec un véhicule pharmaceutique convenable.

12. Procédé de préparation d'un composé chimique selon l'une quelconque des revendications 1 à 6, caractérisé en ce que

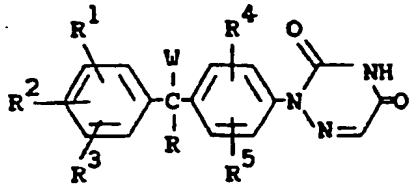
i) on élimine le groupe E d'une triazadione intermédiaire de formule



(III)

dans laquelle E représente un groupe attracteur d'électrons, ladite élimination étant réalisée à des températures plus élevées, le cas échéant en présence d'un acide, ledit acide étant éventuellement utilisé comme solvant et, éventuellement, le cas échéant, en présence d'un solvant inerte vis-à-vis de la réaction; ou

ii) on fait réagir un intermédiaire de formule

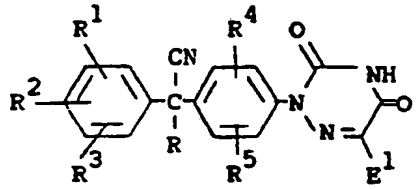


(VI)

dans laquelle W représente un groupe partant réactif, avec un cyanure, le cas échéant en présence d'un solvant inerte vis-à-vis de la réaction.

13. Procédé selon la revendication 12, dans lequel E est un groupe carboxyle, et W est un groupe halogéno, méthylsulfonyloxy ou 4-méthylphénylsulfonyloxy.

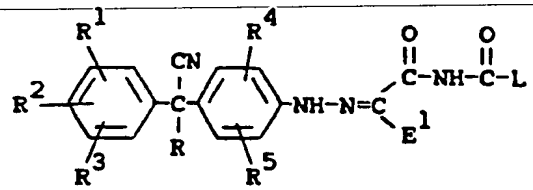
14. Procédé selon la revendication 13, dans lequel l'intermédiaire (III) dans lequel E désigne un groupe carboxyle est produit par hydrolyse d'un intermédiaire de formule



(III-a)

dans laquelle $E^1$ est un groupe cyano, alkyl(en $C_1$—$C_6$) oxycarbonyle ou amido.

15. Procédé selon la revendication 14, dans lequel l'intermédiaire de formule (III-a) est produit par une réaction de cyclisation à partir d'un intermédiaire de formule



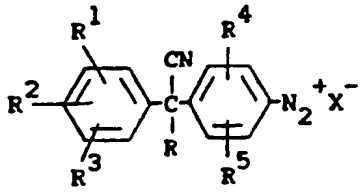
(II-a)

dans laquelle L est un groupe partant réactif.

16. Procédé selon la revendication 15, dans lequel L est un groupe alkyloxy en $C_1$—$C_6$ ou halogéno, et dans lequel la réaction de cyclisation est réalisée dans un milieu acide.

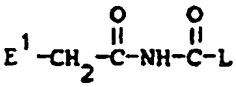
17. Procédé selon la revendication 16, dans lequel le milieu acide est l'acide acétique en présence d'acétate de métal alcalin.

18. Procédé selon la r vendication 15, dans lequ l l'intermédiaire d formule (II-a) est pr duit par réaction d'un diaz nium de formule



(VII)

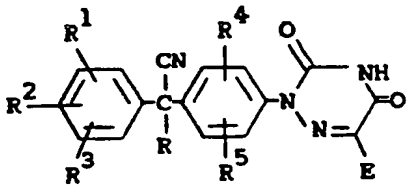
dans laquelle $X^-$ est un anion provenant d'un acide, avec un intermédiaire de formule



(VIII)

19. Procédé selon la revendication 18, dans lequel $X^-$ est un halogénure, L est un groupe alkyloxy en $C_1$—$C_6$ et $E^1$ est un groupe cyano.

20. Composé chimique de formule

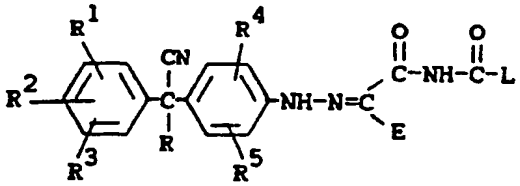


(III)

ses sels d'addition d'acide et ses formes stéréoisomères éventuelles, dans lequel R, $R^1$, $R^2$, $R^3$, $R^4$, $R^5$ sont tels que définis dans la revendications 1, et E est un groupe attracteur d'électrons choisi dans le groupe constitué par les radicaux carboxyle, suylfonyloxy, sulfinyloxy, amido, cyano, alkylsulfonyle en $C_1$—$C_6$, phénylsulfonyloxy, alkyl (en $C_1$—$C_6$)-phénylsulfonyloxy, halogénophénylsulfonyloxy et alkyl(en $C_1$—$C_6$)oxycarbonyle.

21. Composé chimique selon la revendication 20, dans lequel E est un groupe carboxyle, cyano, alkyl (en $C_1$—$C_6$)oxycarbonyle ou amido.

22. Composé chimique de formule



(II)

ses sels d'addition d'acide et ses formes stéréoisomères éventuelles, dans lequel R, $R^1$, $R^2$, $R^3$, $R^4$, $R^5$ sont tels que définis dans la revendications 1, et E est un groupe attracteur d'électrons choisi dans le groupe constitué par les radicaux carboxyle, sulfonyloxy, sulfinyloxy, amido, cyano, alkylsulfonyle en $C_1$—$C_6$, phénylsulfonyloxy, alkyl(en $C_1$—$C_6$)-phénylsulfonyloxy, halogénophénylsulfonyloxy et alkyl(en $C_1$—$C_6$)oxycarbonyle.

23. Composé chimique selon la revendication 22, dans lequel E est un groupe carboxyle, cyano, alkyl(en $C_1$—$C_6$)oxycarbonyle ou amido.